REMARKS

Reconsideration of the rejection of all claims is respectfully requested in view of the above amendments and the following remarks.

Claim Amendments

The chemical structures in claims 1 and 11 have been amended to insert a hydrogen on the indole nitrogen to address the "open valency" issue asserted by the Examiner. It is believed that the meaning of the original structures would have been readily understood by the skilled person such that this amendment should not be necessary, but in any event the fact that the indole valency is not open but satisfied by a hydrogen (whether or not shown) clearly supports this amendment whereby the hydrogen is shown, as requested by the Examiner.

Claim 1 has also been amended to remove "hydrogen" from the scope of R^5 and to remove "oxo" from the scope of R^1 for reasons further explained below in context of the claim rejections.

The introductory "A compound" in the dependent claims has been changed to "The compound," which is believed to be more appropriate under US Practice. The dependencies of certain of the dependent claims has also been adjusted to eliminate any improper multiple dependencies and to reduce the effective number of claims.

Claim 4 has been cancelled as not being within the scope of amended independent claim 1.

In compound claim 10, the 1st, 2nd, 5th and 6th compounds have been deleted as not falling within the scope of claim 1 as amended above.

Claims 12 and 14 have been cancelled as being in a "use" format not generally accepted under US practice.

Method claim 15, directed toward a method of treating a Factor Xa mediated disease or condition, has been cancelled and replaced with new method claim 16, more specifically directed toward a method for producing an antithrombotic or anticoagulant effect in a warm

blooded animal, as demonstrated in *in vitro* and *in vivo* assays c) and d), which provide support and enabling disclosure for new claim 16.

The above amendments are being made without waiver or prejudice to Applicants' right to prosecute any of the subject matter deleted thereby in one or more continuing applications.

It should be clear from the above that all claim amendments are supported by the specification as filed, entry thereof is respectfully requested. Following entry of these amendments, claims 1-3, 5-11, 13 and 16 are pending in this application.

Claim Rejections - 35 USC § 112, Second Paragraph

Claims 1-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically the Examiner asserts that:

i) The indole nitrogen has an open valency, and requests appropriate correction "because the structural formula is not complete."

ii) One of the possibilities of R^1 is oxo, which is said to not be possible and therefore deletion is required.

iii) Claim 12 is a duplicate claim in that "the intended use of a compound in a claim drawn to a compound does not add any limitation and does not have patentability weight."

While Applicants do not necessarily agree with these grounds for rejection, they are all believed to have been overcome or obviated by the above amendments. Specifically:

i) Each structural formula in the claims showing an indole has been amended to show the hydrogen present on the indole nitrogen. The undersigned will undertake to likewise amendment the structural formulae in the specification as soon as allowable subject matter is indicated.

ii) "Oxo" has been removed from the definition of R^1.

iii) Claim 12 has been cancelled as being in a use format not generally accepted under US practice, and this ground for rejection has therefore been obviated.

The rejection of claim 14 under 35 U.S.C. § 112 and § 101 as being in a "use" format has been obviated by the cancellation of claim 14.

Claim Rejections - 35 USC § 112, First Paragraph

Claim 15 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, in that the claim allegedly contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. In particular the Examiner asserts that Applicants "have not provided what is being treated by claim 15, who the subject is, how one can identify said subject (i.e. how one can identify a subject in need), given no specific dose, given no specific dosing regimen, given no specific route of administration, and do not specify what diseases or symptom they intend to treat."

Although Applicants do not agree with the Examiner's assertions, claim 15 has been cancelled and replaced with more specific method of treatment claim 16 in an effort to advance the prosecution of this application to allowance. It is believed that claim 16 is fully enabled by the specification, particularly when considered in context of the therapeutic purpose for which the presently claimed compounds are directed.

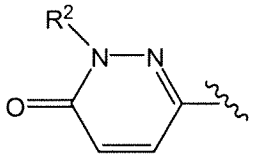
Claim 16 is directed toward a method for producing an antithrombotic or anticoagulant effect in a warm-blooded animal in need thereof comprising administering an effective amount of a compound of formula (I) as defined in claim 1 or claim 10. Persons skilled in the art are well aware of medical conditions, circumstances and patients wherein the possibility of undesirable blood coagulation or thrombosis is at an elevated risk and an anti-thrombotic or anticoagulant is needed. The antithrombotic and anticoagulant effect of compounds of the invention is and can be identified, *e.g.*, by the methods of assay c) and/or assay d). The amounts and methods of administration are discussed at specification pages 17 and 18, and it is common practice to titrate a given patient to determine the dose needed by the particular patient and the particular circumstance. It is therefore respectfully submitted

that the skilled person is sufficiently enabled by the guidance and methodology provided in the specification, taken together with the skill and knowledge in the possession of, or readily available to, such person, to be able to use the method as claimed in claim 16.

Claim Rejections - 35 USC § 103

Claims 1-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Caulkett et al. (WO 99/57113). The Examiner asserts that the Caulkett teaches a generic group of compounds which embraces applicants' claimed compounds, pointing to page 2 of the reference, compounds of formula (I) and definitions for A, B and D. However, it is respectfully submitted that the reference teaches a *very broad* genus relative to the *very narrow* genus of the present claims, and moreover Caulkett teaches *away* from this very narrow genus and the specific compounds as presently claimed. Nevertheless, in order to even further distinguish the present claims from the disclosure of Caulkett, claims 1 and 10 have been amended further limit the scope of substituent R^2 by removing "amino" from the definition of R^2 and removing "hydrogen" from the definition of R^5.

In particular, the compounds as presently claimed necessarily have in the position of the Caulkett ring "A" the specific 2-substituted-2H-pyridazin-3-one group:



wherein R^2 is a mandatory, relatively narrow scope of substituents that does not encompass an amino group or a simple alkylene substituent. Caulkett, on the other hand, broadly defines ring "A" at page 2 as being a 5- or 6-membered monocyclic aromatic ring containing 1, 2 or 3 ring heteroatoms selected from nitrogen, oxygen and sulphur atoms and is unsubstituted or substituted by one, two or three atoms or groups selected from a relatively broad group of possible substituents. Caulkett does define a more preferred scope of ring "A" and its possible substituents at page 6 as follows:

> Preferably A is an optionally substituted 5- or 6-membered monocyclic aromatic ring containing 1, 2 or 3 ring nitrogen atoms. Preferably A is a pyridyl, pyrimidinyl, imidazolyl or pyridazinyl ring for example 2-pyridyl, 3-pyridyl, 4-pyridyl, 3-pyridazinyl, 4-pyridazinyl, 4-pyrimidinyl, 5-pyrimidinyl, 1-imidazolyl, 2-imidazolyl or 4-imidazolyl. Of these 4-pyrimidinyl, 4-pyridazinyl, 1-imidazolyl, 4-imidazolyl and 4-pyridyl are preferred.
>
> Preferred substituents of A are C_{1-4}alkyl, oxo, amino and halo. Preferably substituents are C_{1-4}alkyl, amino and halo. Preferably A is unsubstituted.

(Caulkett *et al.*, page 6, lines 12; emphasis added). Of the exemplified compounds wherein A is a pyridazinyl ring, only Example 10 (particularly relied upon by the Examiner) has a 6-oxo substituent on the pyridazinyl ring. Compounds 14-20 of Example 11 also have a pyridazinyl ring at the "A" position, but the only substituents on the pyridazinyl ring are a 6-hydroxy in compounds 14, 15 and 16, a 6-dimethylamino in compound 17, a 6-chloro in compound 18, a 6-amino in compound 19 and a 6-methylamino in compound 20. Moreover, there is no specific teaching or exemplification of any substituent on either nitrogen of this pyridazinyl ring.

In contract, the present claims require a 6-oxo substituent on the pyridazinyl ring, and also require an R^2 substituent on the ring nitrogen adjacent to the oxo-substituted carbon. Moreover, the compounds as presently claimed do not encompass a C_{1-4}alkyl, amino or halo group (the preferred groups on any generic "A" ring" of Caulkett) or a hydroxy, amino or halo group as at the 6-position of the pyridazinyl ring of Caulkett compounds 14-20 of Example 11.

Therefore, although Caulkett exemplifies one compound having a 6-oxo group on a pyridazinyl ring at the position of ring A, Caulkett *teaches away* from the presently claimed compounds in that:

- Caulkett specifically prefers that ring "A is unsubstituted";

- Where a pyridazinyl ring "A" is substituted in the Caulkett examples, the only pyridazinyl ring "A" substituents are at the 6-position, and are *only* an oxo, hydroxy, amino or halo group; and
- Caulkett does not teach or suggest that *any* substituent be placed on a ring nitrogen of the pyridazinyl ring.

Thus, Caulkett teaches away from the presently claimed compounds, in that the presently claimed compounds *must have both* a 6-oxo substituent *and* a R^2 substituent on a ring nitrogen of the pyridazinyl ring "A", and the permissible pyridazinyl ring R^2 substituents *do not include* the alkyl, hydroxy, amino or halo groups indicated as preferred on any of the generically disclosed "A" rings.

Accordingly, it is respectfully submitted that the Caulkett reference, by teaching away from the presently claimed compounds, does not give rise to *prima facie* obviousness, and that this ground for rejection should be withdrawn.

Conclusion

All grounds for rejection having been specifically addressed and, it is believed, overcome by the above amendments and remarks, it is respectfully submitted that all claims are now in condition for allowance, and a notice to that effect is requested. However, if any issues remain unresolved, it is suggested that the Examiner telephone the undersigned at the number given below in order to expedite the resolution of same and allowance of this application.

EXCEPT for issue fees payable under 37 C.F.R. § 1.18, the Director is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit

Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully Submitted,
Morgan Lewis & Bockius LLP

Date: March 19, 2008 By: _____

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